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Inventor:	Masahiko Hattori 2-7-39 Kita Tamiya, Tokushima-shi, Tokushima Pref.
"	Hiroaki Yamada 48-5 Aza Meishin, Naka-mura, Kitajima-machi, Itano-gun, Tokushima Pref.
"	Yoshito Kiuchi 5-8 Sako Samban-cho, Tokushima-shi, Tokushima Pref.
"	Yuichi Iida 1-8-53 Kita Okinosu, Tokushima-shi, Tokushima Pref.
"	Megumi Fujitani 463-10 Kagasuno, Kawauchi-cho, Tokushima-shi, Tokushima Pref.
Applicant:	Taiho Yakuhin Kogyo Co., Ltd. 1-27 Kanda Nishiki-cho, Chiyoda-ku, Tokyo
Agent:	Hideji Saegusa, Patent Attorney (and 2 others)

Specifications

Title of Invention: Composite anti-tumor preparation

Claims:

(1) A composite anti-tumor preparation characterized in that it is composed of a non-enteric-coated composition containing uracil and an enteric-coated composition containing tegafur.

(2) A composite preparation in accordance with Claim 1, in which the non-enteric-coated composition containing uracil contains crystalline cellulose.

Detailed Explanation of Invention:

Field of Use in Industry

This invention concerns a composite anti-tumor preparation.

Prior Art

It has been confirmed that, when uracil is used together with a 5-fluorouracil (5-FU) derivative, the anti-tumor activity of the 5-FU derivative is synergistically potentiated; compositions of tegafur and uracil have been frequently used as oral agents which have excellent anti-tumor efficacies, for example, as non-enteric-coated capsules. However, tegafur has the drawback that it produces, as its principal side effects, digestive organ symptoms such as anorexia, nausea and vomiting, diarrhea, and stomatitis.

Problem Which This Invention Seeks to Solve

The purpose of this invention is to provide a clinically useful composition of uracil and tegafur with diminished side effects.

Means of Solving the Problem

The inventors performed careful studies with the purpose of developing an anti-tumor preparation in which uracil and tegafur are compounded and which reduces the digestive organ side effects, such as loss of appetite, nausea and vomiting, diarrhea, and stomatitis, as well as keeping the blood level of 5-FU, an active metabolite of tegafur, high.

As a result, they observed that when a composition of tegafur and uracil is made into an enteric-coated preparation, the uracil does not necessarily reach a sufficiently high blood level, and the blood level of 5-FU, an active metabolite of tegafur, is lowered.

As a result of further studies, the inventors discovered that the blood level of 5-FU can be maintained by making a composite preparation of tegafur and uracil that is composed of a non-enteric-coated composition preparation containing uracil and an enteric-coated preparation containing tegafur, and a preparation which is clinically excellent, with reduced side effects. In this way, this invention was perfected.

That is, this invention concerns a composite anti-tumor preparation that is characterized by the fact that it is composed of a non-enteric-coated composition containing uracil and an enteric-coated composition containing tegafur.

The non-enteric-coated uracil composition in the composite agent of this invention can take various publicly-known formulation forms, for example, solid oral formulations such as tablets, granules, capsules, fine granules, and powdered drugs. These can be produced according to customary publicly-known formulation methods, such as adding excipients and, if desired, disintegrants, binders, lubricants,, etc., after which the formulations are produced by the ordinary methods. Publicly known excipients, disintegrants, binders, and lubricants can be used, either individually or in combinations of two or more. Specific examples of these excipients are milk sugar, white sugar, glucose, sucrose, starches, crystalline cellulose, etc. Specific examples of these disintegrants are carboxymethyl cellulose or its calcium salt, hydroxypropyl cellulose with a low degree of substitution, starches, hydroxypropyl starch, dextrin, etc. Specific examples of these binders are methylcellulose, ethyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose sodium salt, polyvinyl pyrrolidone, hydroxypropyl cellulose, etc. Specific examples of these lubricants are talc, stearic acid, stearic acid salts, waxes, light anhydrous silicic acid, etc. In addition, if desired, one may also use coating agents such as hydroxypropylmethyl cellulose and hydroxypropyl cellulose.

It is desirable for the non-enteric-coated composition containing uracil used in this invention to be prepared by compounding crystalline cellulose with uracil. Various commercial products can be used as the crystalline cellulose, either individually or as a mixture. The quantity of crystalline cellulose used is preferably 10–50%, and especially preferably 20–40% (by weight) with respect to the uracil. A still more useful composition can be made by using crystalline cellulose together with the aforementioned disintegrants. Desirable quantities of the disintegrant used in this case are 60% or less of the crystalline cellulose.

In the non-enteric-coated composition containing uracil used in this invention, the quantity of uracil compounded should be in the range of 20–90%, preferably 40–85% (by weight) of the total non-enteric-coated composition.

The enteric-coated composition containing tegafur that is compounded in the composite preparation of this invention can take various publicly-known formulation forms, for example, solid oral formulations such as tablets, granules, capsules, fine granules, and powdered drugs. These can be produced according to customary publicly-known formulation methods, such as adding excipients, enteric coating agents, and, if desired, disintegrants, binders, lubricants, etc., after which the formulations are produced by the ordinary methods. Publicly known excipients, disintegrants, binders,

and lubricants can be used, either individually or in combinations of two or more; the examples mentioned above can be used. Examples of these enteric coatings are hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, methacrylate copolymer-L, methacrylate copolymer-LD, etc.

Granules are an example of a desirable pharmaceutical form of the enteric-coated composition containing tegafur.

Desirable quantities of tegafur compounded in the enteric-coated composition containing tegafur used in this invention are in the range of 10–70%, preferably 30–65% (by weight).

The composite preparation of this invention can be obtained by compounding or formulating the aforementioned non-enteric-coated composition containing uracil and the enteric-coated composition containing tegafur.

The proportions of the enteric-coated composition containing tegafur and the non-enteric-coated composition containing uracil in the composite preparation of this invention vary according to what is necessary, and cannot be stated in general, but they are ordinarily determined by the quantity of tegafur in the enteric-coated composition and the quantity of uracil in the non-enteric-coated composition. Quantities of uracil in the range of 0.02–10 mol, preferably 0.01–10 mol, per mole of tegafur may be used.

The composite preparation of this invention can be administered by administering the respective compositions separately, or the compositions may be compounded together beforehand and formulated in one of various kinds of administration-unit forms, after which this preparation is administered. The administration-unit form may be, for example, solid oral administration forms, such as granules, capsules, tablets, fine granules, and powdered drugs, or a preparation that combines them. They may be formulated by customary methods. When this administration-unit form is formulated, the aforementioned excipients, disintegrants, binders, lubricants, etc., may be added as desired, after which the formulation may be prepared by customary methods.

The quantity of tegafur contained in the composite preparation of this invention should be in the range of 50–250 mg per unit dose.

The composite preparation obtained in this manner can be used as an anti-tumor drug; its dose varies with the symptoms, body weight, age, sex, etc., of the patient, and cannot be designated in general, but ordinarily, for example, it may be administered in the range of 1–30 mg/kg, in capsules, per day for an adult. This dosage may be divided into 1–4 parts per day.

Working Examples

Working and experimental examples of this invention will be shown below.

Production Example 1: Non-enteric-coated uracil granules

Uracil	224 mg
Crystalline cellulose	53 mg
Carboxymethyl cellulose calcium salt	16 mg
Polyoxyl 40 stearate	4 mg
Hydroxypropyl cellulose	3 mg
Total	300 mg

The uracil, crystalline cellulose, carboxymethyl cellulose calcium salt, polyoxyl 40 stearate, and hydroxypropyl cellulose were mixed in the proportions shown above and extruded to form granules. In this way, non-enteric-coated uracil granules (granules 1) were prepared.

Production Example 2: Non-enteric-coated uracil capsules

Uracil	145 mg
Milk sugar	153 mg
Crystalline cellulose	40 mg
Hydroxypropyl cellulose	10 mg
Magnesium stearate	2 mg
Total	350 mg

The uracil, milk sugar, crystalline cellulose, and hydroxypropyl cellulose were mixed in the proportions shown above. Water was added and this mixture was extruded to form granules. After they dried, the magnesium stearate was added and the result was packed into hard gelatin capsules (capsule 1).

Production Example 3: Non-enteric-coated uracil fine granules

Uracil	250 mg
Milk sugar	120 mg
Crystalline cellulose	80 mg
Cornstarch	45 mg
Hydroxypropyl cellulose	10 mg
Hydroxypropylmethyl cellulose	5 mg
Total	500 mg

The uracil, milk sugar, crystalline cellulose, cornstarch, and hydroxypropylmethyl cellulose were mixed in the proportions shown above. Water was added and the result

was granulated. In this manner, a non-enteric-coated uracil fine powder was prepared (fine powder 1).

Production Example 4: Uracil non-enteric-coated tablets

Uracil	75 mg
Milk sugar	55 mg
Crystalline cellulose	20 mg
Magnesium stearate	2 mg
Talc	3 mg
Methyl cellulose	10 mg
Total	165 mg

The uracil, milk sugar, crystalline cellulose, and methyl cellulose were mixed in the proportions shown above. Water was added and the result was granulated. After drying, the talc and the magnesium stearate were added and tablets weighing 165 g, with a diameter of 7 mm, were produced by compression (tablet 1).

Production Example 5: Enteric-coated tegafur granules

Tegafur	100 mg
Crystalline cellulose	15 mg
Carboxylmethyl cellulose calcium salt	20 mg
Polyoxyl 40 stearate	5 mg
Hydroxypropyl cellulose	10 mg
Methacrylate copolymer-LD	50 mg
Total	200 mg

After the granules were prepared by the same method as in Production Example 1, they were coated with methacrylate copolymer LD and enteric-coated tegafur granules (granules 2) were prepared.

Production Example 6: Enteric-coated tegafur capsules

Tegafur	70 mg
Crystalline cellulose	19 mg
Milk sugar	113 mg
Ethyl cellulose	5 mg

Magnesium stearate	2 mg
Methacrylate copolymer-L	50 mg
Total	250 mg

The tegafur, crystalline cellulose, milk sugar, and ethyl cellulose were mixed in the proportions shown above; water was added and the result was extruded to form granules. After drying, the granules were coated with methacrylate copolymer-L and the magnesium stearate was added. After this, the result was packed into hard gelatin capsules (capsule 2).

Production Example 7: Enteric-coated tegafur fine granules

Tegafur	400 mg
Milk sugar	300 mg
Cornstarch	90 mg
Hydroxypropylmethyl cellulose	10 mg
Hydroxypropylmethyl cellulose acetate succinate	200 mg
Total	1000 mg

Granules were formed by the same method as in Production Example 3. After drying, the granules were coated with the hydroxypropylmethyl cellulose acetate succinate, and enteric-coated tegafur fine granules (fine granules 2) were prepared.

Production Example 8: Enteric-coated tegafur tablets

Tegafur	100 mg
Milk sugar	50 mg
Crystalline cellulose	20 mg
Magnesium stearate	2 mg
Hydroxypropyl starch	8 mg
Hydroxypropylmethyl cellulose phthalate	40 mg
Total	220 mg

Tablets weighing 180 mg and with a diameter of 8 mm were compression-molded by the same method as in Production Example 4. They were coated with the hydroxypropylmethyl cellulose phthalate, and enteric-coated tegafur tablets (tablet 2) were prepared.

Reference Production Example 1

The ingredients of the composition shown below were mixed and enteric-coated uracil granules (granules 3) were prepared by the same method as in Production Example 1.

Uracil	224 mg
Crystalline cellulose	17 mg
Carboxymethyl cellulose calcium salt	20 mg
Polyoxyl 40 stearate	4 mg
Milk sugar	12 mg
Hydroxypropyl cellulose	3 mg
Methacrylate copolymer-LD	80 mg
Total	360 mg

Working Example 1: Composite granules

Three hundred milligrams of granules 1 and 200 mg of granules 2 were mixed to produce composite granules A (a product of this invention).

Working Example 2: Composite capsules

One hundred fifty milligrams of capsules 1 and 100 mg of capsules 2 were mixed and packed into hard gelatin capsules to produce composite granules A (a product of this invention).

Working Example 3: Composite tablets

Granules 2	100 mg
Uracil	100 mg
Crystalline cellulose	28 mg
Magnesium stearate	2 mg
Total	230 mg

The granules 2, uracil, crystalline cellulose, and magnesium stearate were mixed in the proportions shown above, and composite tablets A (a product of this invention weighing 230 mg and with a diameter of 9 mm) were produced by compression.

Comparison Example 1

Three hundred sixty milligrams enteric-coated uracil granules (granules 3) and 200 mg enteric-coated tegafur granules (granules 2) were mixed to produce composite enteric-coated granules B (comparison product).

Experimental Example 1

The composite granules A of this invention and the composite granules B (comparison product) were administered orally to beagles and blood samples were drawn over time; the plasma levels of tegafur, uracil, and 5-FU, an active metabolite of tegafur, were measured. The results were compared in terms of pharmacokinetic parameters (AUC (area under the blood level curve) and C_{max})); these are shown in Tables 1 and 2, respectively.

Table 1 (AUC (mg · hr/ml))

	Tegafur	Uracil	5-FU
Granules A	173.450	7.622	0.771
Granules B	176.982	4.810	0.356w

Table 2 (C_{max} (μg/ml))

	Tegafur	Uracil	5-FU
Granules A	18.847	5.173	0.187
Granules B	15.297	2.618	0.077

With composite granules B, in which enteric-coated uracil granules were compounded, markedly low values of the AUC and C_{max} of the uracil and 5-FU were shown; thus, a lowering of their blood levels was observed.

With composite granules A, on the other hand, in which non-enteric-coated uracil granules were compounded, the blood level of 5-FU was kept high, and very good clinical results were obtained.

Experimental Example 2

UFT(TM), a preparation containing non-enteric-coated uracil and non-enteric-coated tegafur, was administered for 2 weeks to a patient (male, 77 years old, body weight 45 kg) who had undergone a laryngeal cancer operation. Immediately after this, the composite granules A of this invention were administered for 2 weeks; the kinds and degrees of side effects were observed. In both cases, the dose was 600 mg/day, as the quantity of tegafur; it was divided into 3 parts and administered orally.

On the 10th day after the UFT administration was started, anorexia appeared; this symptom worsened from then to the 14th day. The patient did not eat a whole meal, or did not eat at all. Furthermore, nausea and vomiting appeared on the 12th day.

Beginning on the 2nd day after the drug was changed to the composite granules of this invention, the nausea and vomiting improved, and the anorexia improved on the 3rd day. These symptoms disappeared on the 4th and 7th days, respectively, and there were no recurrences of them during the administration of the composite granules of this invention.

Experimental Example 3

The composite granules A of this invention were administered for 2 weeks a patient (male, 59 years old, body weight 47 kg) who had undergone a lower pharyngeal cancer operation; after this, UFT was administered for 2 weeks, and the composite granules A of this invention were administered again for 2 weeks. The kinds and degrees of side effects were observed. The dose for both drugs was 600 mg/day, as the quantity of tegafur; it was divided into 3 parts and administered orally.

No side effects were observed during the first administration of the composite granules of this invention. After the drug was changed to UFT, anorexia, nausea, and vomiting appeared; these symptoms continued up to the 14th day thereafter. However, when the drug was changed to the composite granules of this invention again, the nausea and vomiting disappeared completely and the frequency of appearance and degree of the anorexia decreased considerably.

Effectiveness of Invention

The composite preparation of this invention, consisting of a non-enteric-coated composition containing uracil and an enteric-coated composition containing tegafur, can maintain a high blood level of 5-FU, an active metabolite, and considerable reduces the side effects; it is very useful clinically. Therefore, the composite preparation of this invention can be useful as an anti-tumor drug.

Agent: Hideji Saegusa, Patent Attorney